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REMARKS

Formal Matters

Claims 1-9, 11-16, 21, 25, 26, 33-37, 41, 42, 57-66, 68, 69, 74-78, and 80 are pending in the application. Claims 10-17, 22-24, 27-32, 38-40, 43-56, 67, 70-73, and 79 are withdrawn/canceled. Claims 11, 21, 57, 61, 69, and 74 are amended. No new matter is added by the amendments.

Support for the amendments is found throughout the specification, such as at least at page 13, line 38; page 14, lines 16 and 38; page 76, line 27; page 78, line 24 to page 80, line 5; and page 82, lines 15-38 and in the originally filed claims.

Restriction and Election Requirements

Applicants elected group VII drawn to antibody to DR5 in Paper No. 13. Applicants elected four binding sites and SEQ ID NO:10 in Paper No. 14.

Claims 1-15 and 17-80 were pending. Claims 17-20, 27-32, 43-56, 70-72 as well as 3, 10, 67, 73, 74, and 79 were withdrawn from further consideration under 37 CFR 1.142(b) as allegedly drawn to non-elected species, there allegedly being no allowable generic or linking claim. Claims 1, 2, 4-9, 11-15, 21-26, 33-42, 57-66, 68, 69, 75-78, and 80 were examined for the purpose of the instant Office Action to the extent they were drawn to elected species. The Office has not yet expanded the search to determine if the generic claims are allowable because the species had not yet been found allowable.

Applicants respectfully submit that the claims as drawn to the elected species are in condition for allowance. As a result, Applicants respectfully request expansion of the search and reconsideration of the generic claims.

Claim Objections

Claims 21-26, 33-42, and 69 are objected to as not having been amended to reflect the election of species (Paper No. 11) and still allegedly being drawn to multiple inventions instead of the elected invention, i.e. antibody to DR5.

Applicants have amended claims 11, 21, 61, 69, and 74 such that the claims are drawn to an elected species. Claims were withdrawn and/or canceled to comply with restriction and election of species requirements. Applicants respectfully note that under

37 CFR 1.142(b), claims drawn to the non-elected inventions are subject to reinstatement in the event the requirement for restriction is withdrawn or overruled. As a result, claims amended or canceled to comply with the election of species are subject to reinstatement under 37 CFR 1.142(b).

Compliance with 37 CFR §§1.821 - 1.825

The application contains sequence disclosures, such as in claim 11 and Figure 3. A copy of the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures, the Sequence Listing, Certificate under 37 CFR 1.821(f) and (g), and a computer readable form of the Sequence Listing are submitted herewith.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 62 is rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite with respect to recitation of the term "CH4". Applicants respectfully traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

One of ordinary skill in the art readily understands the metes and bounds of an invention reciting a CH4 domain. As Applicants state on page 1, lines 22-23 of the specification with respect to naturally occurring antibodies, "[e]ach heavy chain has at one end a variable domain (VH) followed by a number of constant domains (three or four constant domains, CH1, CH2, CH3 and CH4, depending on the antibody class)." It is well known in the antibody arts that immunoglobulins IgE and IgM comprise CH4 domains. Thus, the metes and bounds of a CH4 domain are readily understood as recited in claim 62.

Having overcome the rejection under Section 112, second paragraph, withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. § 102(a) (Santos et al)

Claims 1, 2, 4-6, 8, 11-15, 66, 68, 75, 76, and 80 are rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Santos et al. (Clin. Cancer Res., 5(10 Suppl):3118s-

3123s (Oct. 1999). Applicants respectfully traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

Santos et al. was available to the public on October 27, 1999 as demonstrated by the enclosed date-stamped journal title page for Clinical Cancer Research volume 5. Applicants conceived and reduced to practice the claimed invention before October 27, 1999 as stated by the instant inventors in the Declaration under 37 CFR § 1.131 submitted herewith. Inventors Kathy L. Miller and Leonard G. Presta state that prior to July 14, 1999, they conceived of and reduced to practice an isolated antibody comprising an Fc region and three or more antigen binding sites amino-terminal to the Fc region. Support for the statement is provided in Exhibit A, attached thereto. Exhibit A is four notebook pages prepared by inventor Kathy L. Miller containing a diagram of a vector for expressing a tetravalent antibody having an Fc region, diagrams of tetravalent antibodies of the invention, and SDS-Page gels of the purified antibodies. Thus, the claimed invention was conceived and reduced to practice before July 14, 1999 and before the date of publication of the Santos et al. reference. As a result, the Santos et al. reference does not anticipate Applicants' claimed invention.

Having overcome the rejection under Section 102(a), the claims are in condition for allowance and withdrawal of the rejection is respectfully requested.

Applicants respectfully remind the Examiner that upon allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim.

Rejection Under 35 U.S.C. § 102(a) (Alt et al.)

Claims 1, 2, 4-6, 8, 11-15, 66, 75, 76, and 80 are rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Alt et al. (FEBS Letters 454:90-94 (1999)). Applicants respectfully traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

Alt et al. was available to the public on July 14, 1999 as demonstrated by the enclosed date-stamped journal title page for FEBS Letters volume 454. Applicants conceived and reduced to practice the claimed invention before July 14, 1999 as stated by

the instant inventors in the Declaration under 37 CFR § 1.131 submitted herewith. Thus, the claimed invention was conceived and reduced to practice before July 14, 1999 and before the date of publication of the Alt et al. reference. As a result, the Alt et al. reference does not anticipate Applicants' claimed invention.

Having overcome the rejection under Section 102(a), the claims are in condition for allowance and withdrawal of the rejection is respectfully requested.

Applicants respectfully remind the Examiner that upon allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim.

Rejection Under 35 U.S.C. § 102(e) (US 6,066,719)

Claims 57-66, 68, 75-78, and 80 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by US 6,066,719 (the '719 patent). Applicants respectfully traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

Applicants' claims 57-66, 68, 75-78, and 80 recite a polypeptide comprising a dimerization domain comprising an Fc region or three or more antigen binding domains. These features are not disclosed in the '719 patent. As a result, the '719 patent does not anticipate Applicants' claims. Withdrawal of the rejection and allowance of the claims is respectfully requested.

Rejection Under 35 U.S.C. § 102(b) (WO 98/41629)

Claims 21-26 are rejected under 35 USC 102(b) as allegedly being anticipated by WO 98/41629. Applicants respectfully traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

Claims 22-24 are canceled without prejudice to later prosecution and merely to comply with an election of species. Applicants respectfully remind the Examiner that upon allowance of a generic claim, the claims, including claims canceled or amended due to the election of species, will be considered with respect to additional species which are

written in dependent form or otherwise include all the limitations of an allowed generic claim.

Applicants claim an isolated antibody comprising an Fc region and three or more antigen binding sites amino-terminal to the Fc region, wherein the antibody binds a DR5 receptor. The WO 98/41629 references discloses a DR5 receptor, but does not suggest or disclose an isolated antibody comprising an Fc region and three or more antigen binding sites amino-terminal to the Fc region. As a result, the WO 98/41629 reference does not anticipate Applicants' claimed invention under Section 102(b). Withdrawal of the rejection and allowance of the claims is respectfully requested.

Rejection Under 35 U.S.C. § 103(a) (Santos et al., US6066719)

Claim 7 is rejected under 35 USC 103(a) as allegedly unpatentable over Santos et al. (supra) as applied to claim 1 and 8 in the Office Action and further in view of US Patent 6,066,719. Applicants traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

Applicants' instant invention of an isolated antibody comprising an Fc region and three or more antigen binding sites amino-terminal to the Fc region was conceived and reduced to practice before the publication of Santos et al., as noted above and in the enclosed Declaration under 37 CFR 1.131 and signed by the inventors. Thus, the Santos et al. reference is not prior art to the instant claims.

The '719 patent issued May 23, 2000 from patent application 08/811,757, filed March 6, 1997, which was a continuation of patent application 08/425,763, filed April 20, 1995. The '719 patent qualifies as prior art only under Section 102(e). The '719 patent is not properly considered prior art under 35 USC 103(c). A reference that is prior art only under 35 USC 102(e) cannot be used, according to 35 USC 103(c), in an obviousness rejection if the subject matter of the cited reference and the climed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. A clear statement of entitlement to the prior art exclusion by Applicants or a registered practitioner is a sufficient evidence to establish the prior art exclusion (Examination Guidelines for 35 USC 102(e) (as amended and revised) at IV(5); 1266 TMOG 80, January 14, 2003).

Applicants hereby make a clear statement of entitlement to exclude the '719 patent as prior art as provided by 35 USC 103(c). The '719 patent and the present patent application were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Neither the Santos et al. nor the '719 patent are prior art to Applicants' invention under 35 USC 103(a). Withdrawal of the rejection and allowance of the claims is respectfully requested.

Rejection Under 35 U.S.C. § 103(a) (Santos et al., US6066719)

Claim 9 is rejected under 35 USC 103(a) as allegedly unpatentable over Santos et al. (supra) as applied to claim 1 and 8 in the Office Action and further in view of US Patent 6,066,719. Applicants traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

For the reasons provided herein above, neither the Santos et al. nor the '719 patent are prior art to Applicants' invention under 35 USC 103(a). Withdrawal of the rejection and allowance of the claims is respectfully requested.

Rejection Under 35 U.S.C. § 103(a) (WO98/41629, US6066719)

Claims 33-42 are rejected under 35 USC 103(a) as allegedly unpatentable over WO98/41629 as applied to claims 21-26 above and further in view of either dUS6066719 (supra) or Santos et al. (supra). Applicants traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

Claims 38-40 are canceled without prejudice to later prosecution and merely to comply with an election of species. Applicants respectfully remind the Examiner that upon allowance of a generic claim, the claims, including claims canceled or amended due to the election of species, will be considered with respect to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim.

For the reasons provided herein above, the '719 patent is not prior art to Applicants' invention under 35 USC 103(a). Further, the WO98/41629, which discloses a DR5 receptor, does not disclose Applicants' claimed invention of an isolated antibody

comprising three or more antigen binding sites. As a result, the rejection of claims 33-42 should be withdrawn. Allowance of the claims is respectfully requested.

Nonstatutory Double Patenting Rejection (US6066719)

Claims 57-62 and 65 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claim 5 of US6066719. Applicants respectfully traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

Applicants' claim a polypeptide chain comprising a VH-CH1-flexible linker-VH-CH1-dimerization domain or a VH-CH1-VH-CH1-dimerization domain, wherein the dimerization domain comprises an Fc region. Applicants further claim an isolated antibody comprising a dimerization domain and three or more antigen binding sites amino-terminal thereto.

Claim 5 does not claim these features of the instant invention. As a result, the rejection should be withdrawn. Allowance of the claims is respectfully requested.

SUMMARY

Claims 1-9, 11-16, 21, 25, 26, 33-37, 41, 42, 57-66, 68, 69, 74-78, and 80 are pending in the application. Claims 10, 17-20, 22-24, 27-32, 38-40, 43-56, 67, 70-73, and 79 are withdrawn/canceled without prejudice to later prosecution. Claims 11, 21, 57, 61, 69, and 74 were amended without the addition of new matter. The claims are in condition for allowance with respect to the claimed species. Because Applicants are entitled to reconsideration of the claims upon allowance of a generic claim, Applicants request that the claims are considered with respect to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim.

If in the opinion of the Examiner, a **telephone conference** would expedite the prosecution of the subject application, the Examiner is **strongly encouraged** to call the undersigned at the number indicated below.

This response/amendment is submitted with a transmittal letter and petition for a three-month extension of time and fees. In the unlikely event that this document is separated from the transmittal letter or if fees are required, applicants petition the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Respectfully submitted,
GENENTECH, INC.

Date: September 26, 2003

By: _____
Deirdre L. Conley, Ph.D.
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Doc. 141705

Clean Set of All Pending Claims

September 26, 2003

1. An isolated antibody comprising an Fc region and three or more antigen binding sites amino-terminal to the Fc region.

2. The antibody of claim 1 comprising four antigen binding sites.

4. The antibody of claim 1 comprising a polypeptide chain, wherein the polypeptide chain comprises two or more variable domains.

5. The antibody of claim 4 wherein the polypeptide chain comprises VD1-$(X1)_n$-VD2-$(X2)_n$-Fc, wherein VD1 is a first variable domain, VD2 is a second variable domain, Fc is one polypeptide chain of an Fc region, X1 and X2 represent an amino acid or polypeptide, and n is 0 or 1.

6. The antibody of claim 5 comprising two or more polypeptide chains, each comprising VD1-$(X1)_n$-VD2-$(X2)_n$-Fc.

7. The antibody of claim 1 comprising at least one polypeptide chain with the formula:

   (c) VH-CH1-flexible linker-VH-CH1-Fc region chain; or

   (d) VH-CH1-VH-CH1-Fc region chain.

8. The antibody of claim 1 comprising at least two light chain variable domain polypeptides.

9. The antibody of claim 8 wherein the light chain variable domain polypeptides further comprise a CL domain.

11. (Once Amended) The antibody of claim 7 wherein the flexible linker comprises the peptide gly-ser-gly-ser (SEQ ID NO:10).

12. The antibody of claim 1 which is internalized faster than a bivalent antibody by a cell expressing an antigen to which the antibodies bind.

13. The antibody of claim 1 which is an agonist antibody.

14. The antibody of claim 1 which induces apoptosis.

15. The antibody of claim 1 wherein the three or more antigen binding sites all bind the same antigen.

16. The antibody of claim 1 wherein the three or more antigen binding sites bind two or more different antigens.

21. (Once Amended) The antibody of claim 1 which binds a DR5 receptor.

25. The antibody of claim 21 which is an agonist antibody.

26. The antibody of claim 21 which induces apoptosis.

33. An isolated antibody comprising three or more antigen binding sites, wherein the antibody is capable of binding a receptor in the Tumor Necrosis Factor (TNF) receptor superfamily.

34. The antibody of claim 33 which is not a native sequence IgM or IgA antibody.

35. The antibody of claim 33 which has only one Fc region or lacks an Fc region.

36. The antibody of claim 33 which comprises a polypeptide chain, wherein the polypeptide chain comprises two or more variable domains.

37. The antibody of claim 33 which comprises four antigen binding sites each capable of binding the DR5 receptor.

41. The antibody of claim 33 which is an agonist antibody.

42. The antibody of claim 33 which induces apoptosis.

57. (Once Amended) A polypeptide chain comprising:

(b) VH-CH1-flexible linker-VH-CH1-dimerization domain; or

VH-CH1-VH-CH1-dimerization domain; and

wherein the dimerization domain comprises an Fc region.

58. An isolated antibody comprising the polypeptide chain of claim 57.

59. The antibody of claim 58 further comprising two or more light chain variable domain polypeptides.

60. The antibody of claim 59 wherein the light chain variable domain polypeptides comprise VL-CL.

61. (Once Amended) An isolated antibody comprising a dimerization domain and three or more antigen binding sites amino-terminal thereto.

62. The antibody of claim 61 wherein the dimerization domain is selected from the group consisting of a hinge region, an Fc region, a CH3 domain, and a CH4 domain.

63. The antibody of claim 62 wherein the dimerization domain is a hinge region.

64. The antibody of claim 63 wherein the dimerization domain further comprises a leucine zipper.

65. The antibody of claim 63 comprising a polypeptide chain comprising the formula:

(a) VH-CH1-flexible linker-VH-CH1-hinge region; or

(b) VH-CH1-VH-CH1-hinge region.

66. A polypeptide chain comprising three or more heavy chain or light chain variable domains, wherein each of the variable domains is able to combine with three or more light chain or heavy chain variable domain polypeptides to form three or more antigen binding sites, each directed against the same antigen.

68. The polypeptide chain of claim 66 which comprises four heavy chain variable domains which are able to combine with four light chain variable domain polypeptides to form four antigen binding sites directed against the same antigen.

69. (Once Amended) The polypeptide chain of claim 66 wherein the antigen is a DR5 receptor.

74. (Once Amended) The polypeptide chain of claim 68 comprising the formula:

(a) VH-CH1-flexible linker-VH-CH1-flexible linker-VH-CH1;

(b) VH-CH1-flexible linker-VH-CH1-flexible linker-VH-CH1-flexible linker-VH-CH1; or

(c) $(VH\text{-}CH1)_n$, wherein n is three or four.

75. An isolated antibody comprising the polypeptide chain of claim 66.

76. The isolated antibody of claim 75 further comprising the three or more light chain or heavy chain variable domain polypeptides.

77. The isolated antibody of claim 76 comprising three or more light chain variable domain polypeptides, each comprising VL-CL.

78. The isolated antibody of claim 77 comprising four light chain variable domain polypeptides, each comprising VL-CL.

80. An immunoconjugate comprising the antibody of claim 75 conjugated with a cytotoxic agent.

81-93 Cancelled.